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been identified as a cause of autosomal dominant cerebellar ataxia.[6] Immunohistochemical studies on cerebellar tissue from an affected member of a family with PKCγ missense mutation showed reduced staining for both PKCγ and ataxin 1 in Purkinje cells, suggesting that there may be a common pathway for PKCγ and polyglutamine-related neurodegeneration.[6] This hypothesis is also supported by the fact that in spinocerebellar ataxia type 1 (SCA1) transgenic mice, PKCγ degradation occurs before the onset of ataxia, suggesting that the loss of this protein is important for the Purkinje cell dysfunction observed in SCA1 patients.[5] A link between paraneoplastic and genetic cerebellar ataxia is also illustrated by voltage-gated calcium channel antibodies (VGCC-Ab). VGCC-Ab, especially those directed against the P/Q type VGCC, are mainly associated with Lambert–Eaton myasthenic syndromes (LEMS),[7] which are paraneoplastic in >70% of the patients. Studies have shown that the frequency of cerebellar ataxia in patients with LEMS is higher than that expected by chance, and that LEMS with ataxia is usually associated with cancer.[8] VGCC-Ab against the P/Q type have also been found in patients with small cell lung cancer and PCA without LEMS,[9] suggesting that VGCC could be associated with some cases of PCA. P/Q type VGCCs are highly expressed in the cerebellum, and gene mutations coding for VGCCs have been identified as a cause of autosomal dominant cerebellar ataxia (SCA6).[10] These data showed that PKCγ and P/Q type VGCCs could be associated with cerebellar ataxia as both paraneoplastic antigen and key mutated protein. From these observations, we can draw two conclusions: although PCA-associated antibodies have not definitively been proven to be pathogenic, they can be used as diagnosis markers to classify subtypes of cerebellar ataxia; although some paraneoplastic antibodies can be observed in only one or two patients, identification of the antigens may have important implications in the identification of key proteins, which could be associated with the neuronal injury of patients with sporadic or genetic cerebellar ataxia.

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Prevention of delayed cerebral ischaemia

Prevention of delayed cerebral ischaemia after subarachnoid haemorrhage

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Physiological abnormalities are a worthwhile target

Delayed cerebral ischaemia (DCI) affects more than one quarter of patients between 3 and 14 days after the onset of their aneurysmal subarachnoid haemorrhage, and accounts for about one third of patients who are dead or dependent as a result of the haemorrhage. Despite the importance of DCI, little can be done to prevent it: only calcium antagonists are supported by good evidence, and the effectiveness of nimodipine is modest (20 patients need to be treated to prevent one poor outcome).[1] Future hope is offered only by the window of opportunity between subarachnoid haemorrhage and DCI onset, and sufficient clinical research interest in finding further interventions for the prophylaxis and treatment of DCI.

In trying to discover whether potentially modifiable physiological abnormalities are a worthwhile target for intervention to prevent DCI, the paper by Naidech *et al*[2] (***p 1340***) explores the association between cerebral infarcts on computed tomograms of the brain after aneurysmal subarachnoid haemorrhage and a physiological derangement score at the time of admission to hospital (based on a patient's oxygenation, acidosis, glycaemic control and blood pressure). In contrast with the study that originally derived the physiological derangement score,[3] the present study is small and retrospective, with an overrepresentation of subarachnoid haemorrhages that were severe or located in the posterior circulation. Furthermore, the study used a radiological marker of DCI rather than clinically important outcome data after discharge from hospital. The authors strove to identify cerebral infarcts due to vasospasm, but multivariate analysis found only clinical severity of subarachnoid haemorrhage and physiological derangement score to be associated with cerebral infarcts. However, the size of the study sample precluded the inclusion of other known determinants of DCI (such as prolonged duration of unconsciousness at onset of subarachnoid haemorrhage) and its design did not allow an analysis of the influence of endovascular or surgical treatment.

The study by Naidech *et al*[2] provokes many questions. Might alternative scoring systems using additional variables be better at predicting poor clinical outcome?[4] Might altered physiology

simply be an epiphenomenon reflecting subarachnoid haemorrhage severity? Could physiological derangement at later stages of admission to hospital be even more influential (as is the case for hypomagnesaemia[5])? As vasospasm is neither necessary nor sufficient to account for DCI, retaining the focus on determinants of poor outcome and DCI is likely to be most beneficial for patients. There are many potential targets for prevention of DCI, including endothelial activation, cortical spreading depression, excitotoxicity mediated by raised intracellular calcium, apoptosis, nitric oxide depletion, free radical formation and mitochondrial dysfunction, many of which may be influenced by the physiological abnormalities in the patient.

For now, the correction of some physiological abnormalities (such as hypoxia, hypotension and hyperglycaemia) after aneurysmal subarachnoid haemorrhage seems to be clinical common sense, not least to try and mitigate the major effect on cardiorespiratory function after subarachnoid haemorrhage[4]. This approach further reinforces the importance of multidisciplinary team management, including critical care.[6] To investigate whether DCI could be prevented by more aggressive treatment of physiological derangements would require large randomised controlled trials, in addition to the ongoing clinical trials of magnesium, simvastatin and clazosentan.[4]

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